Claims 4 and 5 have been amended to overcome the formality rejections.

Care has been taken to ensure that no new matter is added to the claims.

Basically, the Examiner rejects Claims 1-14 under 35 U.S.C. §103(a) as being obvious over Sipos (teaching high proportion of alcohol, but covers the area with BAND-AID) in view of Castillo (teaching the anesthetic, but fails to teach the penetration enhancer).

Applicant notes that the Sipos reference requires the use of a BAND AID (column 16, lines 29-39) to cover the area of skin to be treated, thus the reference fails to teach the step of vaporating the volatile solvent, which is essential in the present invention. As a matter of fact, by covering the area to be treated with a band-aid, the reference is teaching away from the present invention.

Regarding the Castillo reference (to present inventor), it fails to teach the fact that a high amount of a volatile solvent will help to enhance the penetration of the anesthetic through the skin. Thus, there is no reason why this inventor, or one skilled in the art following his teaching, should inherently add a high amount of a volatile solvent to his previous topical anesthetic.

Present Invention

First, Applicant discusses the basis for, and the distinguishing features of the present invention.

The use of topical anesthetics has been found useful for superficial skin procedures. Topical anesthetics act via a loss of sensation in the localized area of administration in the body. The mechanism by which topical anesthetics induce their effect, while not having been determined definitively, is generally thought to be based upon the ability to topically interfere with the initiation and transmission of a nerve impulse, e.g., interfering with the initiation and/or propagation of a depolarization wave in a localized area of nerve tissue. But unfortunately, the use of local anesthesia of intact skin for minor procedures is not achieved until at least 60 minutes following application. For more invasive procedures, such as split skin graft harvesting, at least two hours may be required. This delay in onset is a significant disadvantage, as it is a great inconvenience for both patients and medical staff. Such delay is particularly a problem in the area of pediatrics, where any additional time spent awaiting treatment only contributes to the anxiety of the patient.

Another disadvantage of the prior art is that, for deep penetrative effect, it is necessary that the cream be applied under an occlusive dressing. Specifically, a bi-layer of laminate and absorbent cellulose is taped to the area of the skin to be anesthetized. Such a dressing is inconvenient and messy.

Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum and any material on its surface. They must then penetrate the viable epidermis, the papillary dermis, and the capillary walls into the blood stream or lymph channels to be so absorbed; molecules must overcome a different resistance to penetration in each type of tissue. Transport across the skin membrane is thus a complex phenomenon.

However, it is the cells of the stratum corneum, which present the primary barrier to absorption of topical compositions or transdermally administered drugs.

It has now been surprisingly discovered that the above problems can be overcome, and that a topical, transdermal anesthetic comprising lidocaine can be surprisingly enhanced, by the addition of a high proportion of a volatile carrier/penetration enhancer, preferably a low carbon alcohol, to the anesthetic formulation.

The present invention concerns a **method** for applying a topical anesthetic to an area of skin, the method comprising the steps of:

a) incorporating an anesthetic in a lipophilic base into a volatile solvent to form a homogeneous solution;

b) applying the homogeneous solution into the area of skin to be treated; and

c) **evaporating** the volatile solvent from the homogeneous solution;

wherein the volatile solvent is present in the formulation in amounts between 40 - 80%. (Claim 1)

Upon application to the skin of a patient, and prior to evaporating, the alcohol acts as a penetration enhancer that increases the permeability of the skin, preparing the skin so that the rate at which the anesthetic drug diffuses through the skin and enters the tissues and bloodstream will be increased. The alcohol alters the physiochemical nature of the stratum corneum to reduce its diffusional resistance.

Then, after the skin resistance has been altered, after the skin is initially rendered cool and somewhat anesthetized, and after much of the alcohol has evaporated, the kinetics of the formulation change so that, as the proportion of remaining alcohol is reduced, **a more concentrated anesthetic formulation remains present on the skin, which brings about a more advanced level of anesthetization.**

As a side benefit, the evaporation of the alcohol cools the skin. This causes the patient to feel a soothing, cool, numbing feeling, which psychologically prepares the patient to the effects of the anesthetic. In many patients, this tactile input synergistically enhances pain tolerance.

Thus, by using the formulation of the present invention, the delivery rate of the anesthetic is markedly enhanced, the method of administration remains simple, the incidence of side effects associated with many penetration enhancers is reduced or eliminated, topical irritation is avoided, and the comfort level of the patient is increased as the patient has the perception that the formulation is taking effect.

Office Action

Turning now to the Office Action in greater detail, the paragraphing of the Examiner is adopted.

Paragraphs 1 & 2 (Formalities)

The Examiner rejects Claims 4-5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner indicates that the limitation "said volatile penetration enhancing agent" lacks of antecedent basis.

In response, Applicant has amended the claims to overcome the formalities rejection.

Accordingly, withdrawal of the rejection is respectfully requested.

Paragraphs 1 & 2 (Obviousness)

The Examiner rejects Claims 1-14 under 35 U.S.C. 103(a) as being obvious over Sipos (US 5,993,836) in view of Castillo (US 5,993,836).

According to the Examiner, the claims of the present invention read on a method of applying local anesthetics in lipophilic base in lower alcohols to provide local anesthesia.

The Examiner indicates that Sipos teaches a topical anesthetic composition and a method of obtaining an enhancement of its anesthetic activity by combining the anesthetic agent (e.g. lidocaine, prilocaine, or mixture thereof) with an effective amount of a penetrant accelerator (i.e. cyclohexyl substituted alkanois) in vehicles including lower alcohols (e.g. ethanol, isopropanol); see abstract and claims 1-25, especially column 9, lines 26-27 and examples 7-11. Sipos teaches C5-17 aliphatic alcohols as the said potentiator (e.g. phenyl alcohols); see columns 4-5. For instance, example 9 at column 15, teaches a topical anesthetic gel composition comprising 50%

ethanol, 4% anesthetic agent, and 12% penetrant accelerator (i.e. cyclohexyl alkanols), 5% carbosil, and so on.

The Examiner indicates that the reference fails to teach the use of specific terms such as "lipophilic base," "homogeneous solution," "volatile solvent," "cool sensation," "evaporation," etc.

The Examiner feels that it would have been obvious to one of ordinary skill in the art to modify Sipos into claimed composition because the deficiencies in Sipos are commonly known to any artisan having ordinary skill in the art wherein they are equivalently substitutable due to inherent features, well known techniques, common knowledge, etc.

The Examiner also indicates that Castillo supports this Examiner's allegation by teaching about a topical local anesthetic treatment comprising the steps of incorporating eutectic mixture of lidocaine and prilocaine within a lipophilic base (C 8-18 aliphatic alcohols) to provide rapid-onset, stability and optimal absorption; see abstract and Claim 10. It further teaches suitable additives such as thickeners, thinner, stabilizers, surfactants, etc.

Thus, one would have been motivated to make the local anesthetic containing composition comprising lidocaine or eutectic mixture of lidocaine+prilocaine, incorporated within lipophilic base, mix into volatile solvent (i.e. ethanol, isopropanol) to maximize therapeutic efficacy with optimal dosage, delivery including penetration as evidenced by Sipos; see test comparison with various vehicles; see table V at column 16-17.

The Examiner states that all the minor variations required in dependent claims are properly included in this rejection.

Applicant respectfully traverses.

Applicant notes that the present application includes 4 independent claims, - Claims 1, 9, 10, and 13.

Compared with present Claims 1, 9, and 10, the method of the present invention differs from the Sipos reference in that the claims require: 1) the step of **evaporating the volatile** solvent from the homogeneous solution and 2) the volatile solvent to be present in the formulation in amounts between 40 - 80%.

Regarding point 1

Applicant notes that the Sipos reference requires the use of a BAND AID (column 16, lines 29-39) to cover the area of skin to be treated, thus the reference fails to teach the step of vaporating the volatile solvent, which is essential in the present invention.

The use of a BAND-AID prevents the evaporation of the volatile solvent producing that the alcohol (carrier) and penetration enhancer be co-administered with the anesthetic, thus the alcohol and penetration enhancer pass through the patient's skin at the same time the drug does, which can lead to side effects or, in the case of adulterated alcohol, discomfort.

The disadvantage of BAND-AID becomes obvious when one considers the intended application. BAND-AID is water-impermeable and takes the form of a patch which must be cut to size, and pressed against and adhered onto the skin, thus the use of the BAND-AID allows the alcohol to interact with the patient's skin for extended periods and cause skin irritation and the like.

Another disadvantage associated with the use of a BAND-AID is that the drug is applied "under cover" and gives no direct stimulus (e.g. cooling effect) to the patient. It is difficult

for the patient to know when or if the anesthetic is taking effect. Further, without some form of psychological stimulus, the patient may not become mentally receptive to becoming anesthetized.

In the present invention, the alcohol acts as a penetration enhancer that increases the permeability of the skin, preparing the skin so that the rate at which the anesthetic drug diffuses through the skin and enters the tissues and bloodstream will be increased. The alcohol alters the physiochemical nature of the stratum corneum to reduce its diffusional resistance. Then, after the skin resistance has been altered, after the skin is initially rendered cool and anesthetized, and after much of the alcohol has evaporated, the kinetics of the formulation change so that, as the proportion of remaining alcohol is reduced, a more concentrated anesthetic formulation remains present on the skin, which brings about a more advanced level of anesthetization.

As a side benefit, the evaporation of the alcohol cools the skin. This causes the patient to feel a soothing, cool, numbing feeling, which psychologically prepares the patient to the effects of the anesthetic. In many patients, this tactile input synergistically enhances pain tolerance.

Thus, by using the formulation of the present invention, the delivery rate of the anesthetic is markedly enhanced, the method of administration remains simple, the incidence of side effects associated with many penetration enhancers is reduced or eliminated, topical irritation is avoided, and the comfort level of the patient is increased as the patient has the perception that the formulation is taking effect.

The Sipos reference does not disclose the present invention as presently claimed. As a matter of fact, by covering the area to be treated with a band-aid, the reference is teaching away from the present invention.

Regarding the Castillo reference

Applicant notes that compared with Claims 1, 9, 10, and 13, the reference fails to teach the step of evaporation and the presence of 40-80% alcohol.

Applicant notes that the Castillo reference discloses a topical anesthetic formulation including, e.g., lidocane (15%), prilocane (5%), and dibucaine (0.75%) as anesthetics; phenylephrine as vasoconstrictor; and a lipophilic base. Lidocane and prilocane form an eutectic mixture, and the formulation is incorporated in a lipophilic base. The reference is limited to specific anesthetics, in specific ratios.

Applicant also notes that the reference is silent regarding the use of a penetration enhancer to provide a rapid penetration of the anesthetic. Applicant further notes that Claim 10 requires the use of a higher aliphatic alcohol (C8-18 or an ester). The present invention uses a volatile solvent such as a low carbon alcohol. A C8-18 alcohol cannot be considered as a low carbon alcohol.

In Ex parte Viscardi, 136 USPQ 382. The Applicant discovered that addition of carbon dioxide would remove static electricity. The Examiner rejected the application over a reference, which taught addition of carbon dioxide, but for a different reason. The court held that there is merit in the contention that a reference patent does, as urged by the Examiner, inherently provide carbon dioxide, which will remove

static electricity. However, in an absence of appreciation by patentee (the reference) of the fact that carbon dioxide will remove static electricity, there is no reason why he, or one skilled in the art following his teaching, should inherently adjust the concentration of carbon dioxide for removal of complete static charge; hence, manipulative steps of Applicant's claims do not inherently result from reference's disclosure.

Thus, in the absence of appreciation by patentee Castillo of the fact that a high amount of a volatile solvent will help to enhance the penetration of the anesthetic through the skin, there is no reason why this inventor, or one skilled in the art following his teaching, should inherently add a high amount of a volatile solvent to his topical anesthetic.

Thus, Castillo does not disclose the present invention as presently claimed.

Combining Sipos and Castillo

Numerous decisions require that the prior art contains an express or implicit suggestion that prior art teachings be modified or combined in the manner claimed by the inventor before the inventor's patent claim may be rejected or invalidated for obviousness.

The mere fact it is possible for two isolated disclosures to be combined does not render the result of that combination obvious absent a logical reason of record, which justifies the combination. In re Regel et al. (CCPA 1975) 188 USPQ 136. To properly combine two references to reach a conclusion of obviousness, there must be some teaching, suggestion, or inference in either or both of the references, or knowledge generally available to one of ordinary skill in the art, which

would have led one to combine the relevant teachings of the two references.

The Examiner must be able to point to something in the prior art that suggests in some way a modification of a particular reference or a combination with another reference in order to arrive at the claimed invention. Absent such a showing in the prior art, the Examiner has impermissibly used the Applicant's teaching to hunt through the prior art for the claimed elements and combine them as claimed. In re Laskowski 10 USPQ 2d 1397, 1398 (Fed. Cir. 1989).

While representing an improvement over prior art topical anesthetic formulations, there remains a need for further improvement in delivery rate of the anesthetic, ease of administration, and patient acceptance.

Accordingly, withdrawal of the rejections is respectfully requested.

Favorable consideration and early issuance of the Notice of Allowance are respectfully requested. Should further issues remain prior to allowance, the Examiner is respectfully requested to contact the undersigned at the indicated telephone number.

Respectfully submitted,

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Date: **February 22, 2002**

VERSION WITH MARKINGS TO SHOW CHANGES MADE HEREBY ATTACHED

The Examiner is requested to accept the marked-up version as it is based on the previous version, which when modified as below, produces the clean version submitted with the current amendment.

Please amend the claims as follows:

4. (Once amended) The method according to claim 1, wherein said volatile [penetration enhancing agent] solvent is an alcohol.

5. (Once amended) The method according to claim 1, wherein said volatile [penetration enhancing agent] solvent is selected from the group consisting of isopropyl alcohol and denatured ethyl alcohol.